PUBLIC SUMMARY DOCUMENT

Product: DARUNAVIR ETHANOLATE, film-coated tablets, 300 mg (base), Prezista®

Sponsor: Janssen-Cilag Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought a section 100 (Highly Specialised Drug) PBS listing for darunavir for the treatment, in combination with 100 mg ritonavir and with other anti-retroviral agents, of human immunodeficiency virus (HIV) in antiretroviral treatment experienced patients, who have failed treatment with at least three different anti-retroviral regimens, including two or more protease inhibitor containing regimens.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Darunavir (with ritonavir 100 mg as pharmacokinetic enhancer) was registered by the TGA on 15 March 2007 and is indicated, in combination with other antiretroviral agents, for the treatment of HIV-1 infection in heavily pre-treated adults with evidence of viral replication, who have HIV-1 strains resistant to multiple protease inhibitors.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drug) Private hospital authority required
Treatment, in combination with 100mg ritonavir and with other antiretroviral agents, of human immunodeficiency virus (HIV) infection in antiretroviral treatment experienced patients who have failed previous treatment with at least three different antiretroviral regimens, including two or more protease inhibitor containing regimens.
Treatment failure is defined as either:
a) Evidence of HIV replication, despite ongoing therapy; or
b) Treatment-limiting toxicity to previous protease inhibitors.

See Recommendation and Reasons for the PBAC's view.

5. Clinical Place for the Proposed Therapy

Human immunodeficiency virus (HIV) infection is a chronic, immunosuppressive infection. Without effective anti-retroviral treatment, HIV infection eventually leads to severe immune deficiency and the development of systemic opportunistic infections and cancers that define acquired immune deficiency syndrome (AIDS), and ultimately results in death. In Australia in 2005, more than 900 new cases of HIV infection were diagnosed. While the majority of patients with HIV are receiving highly active anti-retroviral therapy (HAART), factors such as tolerability, drug-drug interactions and cross-resistance to currently available therapies

limit the long-term response to HAART therapy. Patients eventually fail sequential HAART and become highly treatment experienced with persistent viraemia.

Darunavir is a new generation bis-tetrahydrofuran protease inhibitor (b-THFPI), which maintains potency against mutant HIV strains resistant to currently available protease inhibitors (PIs).

6. Comparator

The submission nominated standard care (i.e. one or more of a group of preferred or alternative PIs (atazanavir, lopinavir, fosamprenavir, indinavir, nelfinavir, saquinavir), also used with ritonavir at fourth line) as the main comparator.

Tipranavir was presented as a secondary comparator.

The PBAC considered that the comparison with tipranavir, which was recommended at the March 2007 PBAC meeting, was the more relevant analysis.

7. Clinical Trials

The submission presented as pivotal evidence, two randomised, multicentre, partially blinded, parallel group phase IIb trials (POWER 1 and 2) comparing 600/100 mg darunavir/ritonavir with standard care in HIV-1 infected patients, who were at least 3-class anti-retroviral experienced. These trials are ongoing, with data for up to 48 weeks evaluated by PBAC.

Supportive efficacy and safety data from the POWER-3 study was also presented.

Darunavir was also compared to tipranavir via an indirect comparison of the POWER trials against two randomised, multicentre, open label, parallel group phase III trials (RESIST 1 and 2) comparing 500/200 mg tipranavir/ritonavir with standard care in HIV-1 infected patients, who had three or more PI mutations, over 96 weeks. The 48-week results from these studies were used in the indirect comparison.

The published trials are as follows:

Trial/First author	Protocol title	Publication citation
POWER		
Lazzarin (2006)	TMC114/r provides durable viral load suppression in treatment-experienced patients: POWER-1 and 2 combined Week 48 analysis	16th Int AIDS Conf, 13-18th August, Toronto, Canada (poster)
Hill (2006)	Relative antiviral efficacy of TMC114/r and tipranavir/r versus control PI in the POWER and RESIST studies	12th Ann Conf British HIV Assoc (BHIVA), 29 Mar-1 April, Brighton, UK (poster)
Clotet B et al	Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection	Lancet, April 2007, 246 (9568): 1169 – 1178
RESIST		
Gathe, J et al 2006	Efficacy of the protease inhibitors tipranavir and ritonavir in treatment experienced patients: 24-week analysis from the RESIST-1 trial.	Clin Infect Dis, 43: 1337-1346
Cahn, P et al 2006	Ritonavir-boosted tipranavir demonstrates superior efficacy to ritonavir-boosted protease inhibitors in treatment experienced HIV-infected patients: 24-week results of the RESIST-2 trial	Clin Infect Dis, 43 : 1347-1356

Trial/First author	Protocol title	Publication citation
Combined report of RESIST-1 & 2 studies	Boehringer Ingelheim FDA Briefing Document, 19/Apr/05 (available from FDA website)	
	FDA Evaluation Report on tipranavir (from FDA website)	
Cahn, P 2005	RESIST-1 (R-1) and RESIST-2 (R-2) 48 week meta-analysis demonstrates superiority of protease inhibitor (PI) tipranavir +ritonavir (TPV/r) over an optimised comparator PI (CPI/r) regimen in antiretroviral (ARV) experienced patients	Abstract no. PS3/8, 10th Eur AIDS Conf (EACS), 17-20 Nov, Dublin, Ireland (poster)
Hicks 2006	Durable efficacy of tipranavir-ritonavir in combination with an optimised regimen of antiretroviral drugs for treatment-experienced HIV-1 infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug resistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials	Lancet, 368: 466-475.
Hill 2006	Relative antiviral efficacy of TMC114/r and tipranavir/r versus control PI in the POWER and RESIST studies	12th Ann Conf British HIV Assoc (BHIVA), 29th Mar-1st Apr, Brighton, UK (poster)
Baxter, J et al 2006	Genotypic changes in human immunodeficiency virus type 1 protease associated with reduced susceptibility and virologic response to the protease inhibitor tipranavir	J Virol, 80: 10794-10801

8. Results of Trials

The results of the key trials are summarised below.

DARUNAVIR vs. STANDARD CARE

Pooled results at 24 weeks - darunavir/rtv 600 mg b.i.d vs. Std Care

Study	Proportion of patients with virological response*		Relative risk (RR) & 95% CI	Absolute risk difference (ARD) & 95% CI
	Darunavir (DAR/rtv 600/100 mg BID)	Control: Std Care		
POWER-1	46/60 (76.7%)	15/60 (25.0%)	3.07 (2.00, 4.95)	51.7% (34.8%, 65.3%)
POWER-2	24/39 (61.5%)	6/42 (14.3%)	4.31 (2.09, 9.47)	47.3% (27.0%, 63.8%)
Test for heterogeneity			Q statistic = 0.5487 P = 0.4589	Q statistic = 0.1291 P = 0.7194
Pooled estimate (random effects)			3.35 (2.25, 4.97)	49.9% (38.1%, 61.7%)

*defined as a decrease of 1.0 $\log_{10}$ or more in plasma viral load; RTV = ritonavir

DARUNAVIR vs. TIPRANAVIR

Indirect comparison of proportions of responders for the primary outcome in POWER vs. RESIST trials (48 weeks)

	POWER 1 and POWER 2 48 week pooled data		**RESIST 1 and RESIST 2 48 week pooled data:**	
	Darunavir (DRV/rtv 600/100mg BID) n/N (%)	Control: Std Care n/N (%)	Tipranavir (TPV/rtv 500/200 mg BID) n/N (%)	Control: Std Care n/N (%)
Primary virological response: RNA >= 1 $\log_{10}$ below baseline	67/110 61%	18/120 15%	251/746 33.6%	113/737 15.3%
Relative risk vs Standard Care	3.72*		2.19	
Absolute risk difference vs Standard Care (SE)	45.7% (5.3%)		18.3% (2.2%)	
Indirect comparison (DRV/rtv-control)-(TPV/rtv-control) Relative Risk	1.70 (1.06, 2.72)			
Indirect comparison (DRV/rtv-control)-(TPV/rtv-control) Absolute risk difference	27.4% (16.2%, 38.6%)			

* RR reported as 4.1 (2.6, 6.4) in the Lancet 2007 publication

For PBAC's view of these results, see Recommendations and Reasons.

9. Clinical Claim

The submission also described darunavir as having significant advantages in effectiveness over tipranavir, and having similar or less toxicity. The PBAC accepted this claim.

10. Economic Analysis

A modelled economic evaluation was presented. The choice of the cost-utility approach versus standard care and tipranavir were considered valid.

The resources included were drug costs, diagnostic tests and specialist and GP visits.

The base case modelled incremental discounted cost/extra discounted life year gained (LYG) and quality adjusted life year (QALY) vs. standard care and tipranavir was estimated, in both cases, to be between $15,000 - $45,000.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of patients/year to be < 10,000 in Year 5.

The financial cost/year to the PBS was estimated to be $10 – $30 million in Year 5.

12. Recommendation and Reasons

The PBAC recommended the listing of darunavir on the PBS for the treatment of HIV infection in antiretroviral treatment experienced patients who meet certain criteria on the basis of a high but acceptable incremental cost-effectiveness ratio compared with tipranavir.

The PBAC noted that the submission had nominated standard care as the main comparator and tipranavir as a secondary comparator. As tipranavir was recommended for use in the same patient group by the PBAC at its March 2007 meeting, this was considered the most appropriate comparison.

The PBAC considered darunavir had significant advantages in effectiveness over tipranavir and similar or less toxicity, based on the results at the 48 week time point in the POWER 1 and POWER 2 studies compared to same the time point in the RESIST 1 and RESIST 2 studies. The PBAC's decision regarding the advantages in effectiveness over tipranavir was made in the absence of head-to-head data.

The PBAC noted that the submission calculated the base case modelled incremental discounted cost/extra discounted QALY for darunavir versus tipranavir to be between $15,000 - $45,000 per/QALY, which was considered acceptable by the PBAC.

Recommendation

DARUNAVIR ETHANOLATE, film-coated tablets, 300 mg (base)

Restriction: Private hospital authority required (Highly Specialised Drug)
Treatment, in combination with other antiretroviral agents, and co-administered with 100 mg ritonavir twice daily, of HIV infection in an antiretroviral experienced patient with:
(a) evidence of HIV replication (viral load greater than 10,000 copies per mL), and/or
(b) CD4 cell counts of less than 500 per cubic millimetre.

A patient must have failed previous treatment with, or have resistance to, 3 different antiretroviral regimens which have included:
i) at least 1 non-nucleoside reverse transcriptase inhibitor; and
ii) at least 1 nucleoside reverse transcriptase inhibitor; and
iii) at least 2 protease inhibitors.

Pack Size: 120

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Janssen-Cilag welcomes this decision by the PBAC to provide access to an additional treatment option for Australians living with HIV/AIDS.